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Published in:
Annals of Oncology

DOI:
10.1093/annonc/mdx071

Publication date:
2017

Article type: Original Article

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J. Shamash[1], S.-J. Sarker[1], R. Huddart[2], S. Harland[3], J.K. Joffe[4], D. Mazhar[5], A. Birtle[6], J. White[7], K. Chowdhury [1], P. Wilson[1], M. R. Marshall[1], and S. Vinnicombe[8]

1. Centre for Experimental Cancer Medicine, Barts Cancer Institute, QMUL, UK.
2. Institute of Cancer Research, London, UK.
3. University College London Hospitals, Department of Oncology, London, UK.
4. Huddersfield Royal Infirmary, UK.
5. Addenbrookes' Hospital, Cambridge, UK.
6 Lancashire Teaching Hospitals, UK.
7. Beatson West of Scotland Cancer Centre, UK.
8. School of Medicine, University of Dundee, UK.

Corresponding address:

Dr Jonathan Shamash, MD FRCP
Consultant Medical Oncologist
Barts Cancer Institute, Bart's Health NHS Trust
Queen Mary's School of Medicine and Dentistry
LONDON EC1M 6BQ
E-mail: Jonathan.Shamash@bartshealth.nhs.uk

This is a pre-copyedited, author-produced version of an article accepted for publication in Annals of Oncology following peer review. The version of record J. Shamash, S.-J. Sarker, R. Huddart, S. Harland, J.K. Joffe, D. Mazhar, A. Birtle, J. White, K. Chowdhury, P. Wilson, M. R. Marshall, S. Vinnicombe; A randomised phase III study of 72 hour infusional versus bolus bleomycin in BEP (bleomycin, etoposide and cisplatin) chemotherapy to treat IGCCCG good prognosis metastatic germ cell tumours (TE-3). Ann Oncol 2017 mdx071 is available online at:
https://academic.oup.com/annonc/article/doi/10.1093/annonc/mdx071/3038395/A-randomised-phase-III-study-of-72hour-infusional?rss=1

Abstract

Background: Bleomycin is an integral part of combination chemotherapy in germ cell tumours. Pulmonary toxicity often necessitates drug cessation and death occurs in 1-2% of patients. A continuous infusion of bleomycin might reduce lung toxicity when compared to the conventional weekly boluses given as part of standard BEP chemotherapy.

Patients and Methods: A phase 3 randomised trial was conducted. Two hundred and twelve men with IGCCCG good prognosis metastatic germ cell tumours were randomized in a 1:1 fashion. They were stratified for age, smoking history and renal function. Patients received either conventional BEP with weekly bleomycin (30000 units /week IV bolus) or as a 90000 unit infusion on day 1 over 72 hours. The primary endpoint was CT assessed lung toxicity, secondary endpoints included PFS, changes in lung function testing and quality of life. Repeated measures mixed effects model was used to analyse the data.

Results: CT assessed lung toxicity for the infusional and conventional arm patients were respectively 80% versus 62% at the end of treatment and 54% versus 51% at one year post treatment. There was no significant difference between the two arms for CT assessed lung toxicity (estimated regression coefficient (difference) =1.4, P=0.9, 95% CI:-0.36, 3.16). Older patients had higher toxicity (coefficient=4.81, 95% CI: 3.04, 6.58). Lung toxicity increased after 1 cycle and peaked at end of treatment ($P \leq 0.002$) and then declined. Lung function testing failed to show any differences between the two arms, and did not predict for subsequent lung damage. The median follow-up was 2.5 years. Two-year PFS rate (infusional arm= 93% versus conventional arm=94%; hazard ratio =0.91, 95% CI: 0.33, 2.52) was not significantly different. Cough (P=0.002) but not shortness of breath ($P \geq 0.09$) was associated with bleomycin toxicity.

Conclusions: Infusional bleomycin has no advantage over standard administration. It supports abandoning routine pulmonary function testing, instead the presence of cough should be sought and the early use of CT scanning of the chest to evaluate potential lung toxicity is preferred.

Keywords: germ cell tumour, bleomycin, infusion, lung

Introduction

Most patients with IGCCCG good prognosis metastatic germ cell tumours are cured with 3 cycles of cisplatin, etoposide and bleomycin (BEP). Randomised studies have confirmed cisplatin100mg/m2, etoposide 500mg/m2 and bleomycin 90,000 units per cycle to be optimal [1, 2]. The cisplatin and etoposide may be given over 3 or 5 days [2] and reductions in the dosage of bleomycin or etoposide are associated with poorer overall survival [1, 3]. Bleomycin has long been known to cause unpredictable and occasionally fatal lung toxicity. Prior poor lung function, a smoking history, and impaired renal function may predispose to an increased likelihood of toxicity [4]. Retrospective reports suggest that the damage caused by bleomycin be related to the peak levels of the drug which may be avoided by giving the drug as a continuous infusion [5]. In vivo experiments in animal models support this hypothesis [6].
In a patient group with a good outcome, optimisation of bleomycin may be expected to improve efficacy and reduce toxicity. As the value of pulmonary function testing in this setting has been controversial [7] we wished to see whether pre- treatment pulmonary function testing could identify an at-risk population for development of lung toxicity and whether changes during treatment correlated with the development of CT scan changes. We also wished to determine whether any symptoms associated with the development of bleomycin induced lung injury e.g. shortness of breath, cough, and chest discomfort correlated with CT changes. We therefore performed a randomised trial.

Patients and Methods

Eligible patients were males over 16years old with IGCCCG good prognosis disease (testicular germ cell tumours with metastases but no non-pulmonary visceral sites with tumour markers not exceeding the following AFP 1000ng/ml, hCG, 5000 iU/ml, LDH 1.5x the upper limit of normal).

All patients were staged using CT scanning. The pulmonary parenchyma was assessed using conventional lung settings rather than dedicated high resolution CT of the chest. Patients were required to have adequate renal function (calculated or measured glomerular filtration rate of > 50ml/min). Patients were randomised to receive 3 cycles of 3 day BEP (cisplatin 50mg/m^2 on day 1 and 2, etoposide 166mg/m^2 day 1, 2 and 3) and either conventional bleomycin 30,000 units per week on days 1, 8 and 15 as a 30min intravenous infusion (conventional arm) or a protracted infusion (90,000 units as a continuous intravenous infusion over 3 days on days 1, 2 and 3 of each cycle (infusional arm). Routine use of growth factors was not permitted.. A conventional chest CT, quality of life, and pulmonary function tests were performed immediately prior to the second cycle, at the end of treatment (9 weeks after chemotherapy started), 1 year and 2 years after treatment.

Quality of life assessments used the EORTC QLQC-30 questionnaire with the addition of LC 17 (originally developed for lung cancer, it was used to look for specific symptoms attributable to lung toxicity) [8].

The primary end point of the study was the development of CT assessed lung toxicity attributable to bleomycin. The validated endpoint CT changes were selected, as they, rather than changes in lung function correlate best with long term pulmonary damage [4, 9, 10]. The

secondary endpoints were progression-free survival, overall survival, changes in pulmonary function testing, and quality of life. Pulmonary function tests included an assessment of FEV1, FVC, TlCO and KCO.

Patients were required to give written informed consent. The trial had formal ethical approval (trial reg MREC 3/3/029).

CT review

All the CT scans were anonymised, the reporting radiologist was blinded to treatment allocation and all scans viewed by a single radiologist. The scans were reported as follows. As this was a multicentre trial, scan acquisition varied according to institution, but in all cases, slice thickness was no more than 2.5mm. Where dedicated lungs settings were not provided, a standard edge algorithm was applied. Each lung field was split into an anterior and posterior section (4 in all- right anterior, right posterior, left anterior and left posterior). The degree of CT assessed lung toxicity was graded between 0-3. Grade 1 changes represented subtle fine sub-pleural linear opacity, grade 2 changes – more pronounced than grade 1 but with no coalescence or consolidation. Grade 3 represented more diffuse changes with coalescence [11]. The number or total sections with subpleural changes for each scan examined was noted allowing a percentage of sections with involved changes to be derived, as well as the proportion of grade 2 and 3 changes. The results were summarised in the following format – the percentage of sections showing any damage, the number of sections showing individually grade1, 2 or 3 damage. This was carried out at baseline, day 21, end of treatment and 1 and 2 years post

91 treatment. In some patients changes were present prior to chemotherapy – these were termed
92 baseline changes, their subsequent presence post chemotherapy were therefore not
93 attributable to bleomycin.

94

95 **Statistics**

96 A previous retrospective review of the toxicity encountered when bleomycin was administered
97 as a continuous infusion had suggested a substantial reduction in bleomycin induced changes (a
98 difference of 44%). It was felt to be worthwhile even if the reduction in toxicity were around
99 15%. Therefore a reduction in toxicity from 27% (expected) to 11% required a total of 210
100 patients at the 5% level of significance with 80% power based on a 2-sided test.

101 Randomisation, following 1:1 allocation, was stratified for smoking (smoker vs non-smoker),
102 renal dysfunction (> 80ml/min or ≤80ml/min as calculated by Cockroft and Gault) and age (<30
103 vs ≥30 years) as all these factors have been associated with an increased risk of bleomycin
104 induced lung toxicity [4, 12].

105 To determine the statistical significance of the association between categorical and continuous
106 outcome variables, the Chi-square and Independent samples T-test were used as appropriate.
107 Repeated measures mixed effects models were used to model CT proven lung toxicity as a
108 function of the predictor variables accounting for both fixed effects (stratification factors) and
109 random effect(patient ID). Nonparametric testing for trend was carried out to observe for
110 trends in toxicity grading with time. Pearson's correlation coefficients were used to assess

correlation between lung function variables and lung toxicity at each time point and then linear regression was used for prediction. Association between quality of life (symptoms) and change of lung toxicity (end of treatment - baseline) was studied using two-sample t-test.

Results

Two hundred and twelve patients from 13 sites were randomised (105 in the infusional arm and 107 in the conventional arm), see CONSORT diagram in S1. Table 1 confirms the validity of randomization with the two groups well balanced in terms of baseline characteristics. Thirty-five percent of patients were smokers, 5% had an estimated GFR of < 80ml/min and 53% were over the age of 30. The median follow-up was 2.3 years.

The proportion of patients with CT detected lung toxicity (any, grade ≥2, grade 3) respectively increased from baseline (12.2%, 0%, 0%) to day 21 (29.5%, 2%, 0%) and end of treatment (705%, 34.5%, 5.1%) but improved at 1 year post treatment (52.4%, 4.2%, 0.6%) and 2 years post treatment (47.9%, 2.6%, 0.9%). There was a significant trend for increasing CT defined toxicity after 1 cycle, which peaked at the end of treatment ($P \leq 0.002$).

Thirty percent of patients (n=37) had CT assessed grade 1 toxicity by day 21 and 35% of them increased to grade≥2 toxicity by the end of the treatment. Eighty four (68%) patients showed no evidence of lung toxicity at day 21 but 27% of them went on to develop grade≥2 lung toxicity at the end of treatment.

Those patients with smaller body surface areas (< median) did not have significantly higher toxicity (small BSA: 38% vs higher BSA: 34%, *P*=0.18) at the end of treatment despite the fact that bleomycin dosing was fixed independently of body size.

Treatment comparison:

Table 2 shows that toxicity in the infusional arm was generally higher than the conventional arm and it was significantly higher at the end of treatment (80% vs. 62%, *P*=0.01).

Repeated measures mixed effects analysis, Table 3, shows that there was no significant difference (CI includes zero) in percentage of grade ≥1 toxicity between the two arms (estimated coefficient=1.4; 95% CI: -0.36, 3.16). It confirms that a significantly higher level of grade ≥2 toxicity in the infusion arm (0.92; 0.22, 1.62) mainly at the end of treatment. Baseline toxicity was significant (1 unit increase gave the percentage of grade ≥2 toxicity decrease by a factor of 0.16). Of the stratified factors only age was statistically significant. Patients older than 30 had on an average 4.8 percentage point higher grade ≥1 toxicity but 0.84 percentage point lower grade ≥2 toxicity. Smoking was not associated with baseline damage (*P* = 0.5), nor was it related to the severity and frequency of subsequent bleomycin toxicity (Table 3). The total doses of bleomycin was the same in both groups.

Two-year PFS rate (infusional arm= 92.5% versus conventional arm=94.1%; hazard ratio =0.91, 95% CI 0.33 to 2.52) was not significantly different.

Lung function and CT assessed toxicity:

There was no relationship between pre-existing lung function and subsequent CT assessed toxicity (see Table 4). Pulmonary function declined during treatment and then recovered 1 year post therapy (Figure S2). Table 4 shows that decreased lung function was weakly correlated ($r \approx -0.30$) with increased toxicity only at the end of treatment ($P < 0.05$), especially based on DLCO (kco). Pre-treatment lung function did not predict subsequent development of pulmonary toxicity (all CIs include 0); (Table S1).

Quality of Life (see Table 5)

The quality of life data showed that the development of a dry cough ($P=0.002$) rather than shortness of breath ($P \geq 0.09$) or chest tightness ($P=0.18$) was the only symptom significantly associated with the development of CT assessed lung toxicity. Shortness of breath showed a positive association with the development of CT assessed lung toxicity but was not significant ($P=0.09$).

Discussion

A continuous infusion of of bleomycin over 72 hours was unable to reduce the likelihood of developing pulmonary toxicity compared to conventional administration. There was significantly higher level of grade ≥2 toxicity in patients in the infusion arm, refuting the above

hypothesis. Nevertheless this study has expanded our knowledge as to the timing of development of lung toxicity and the natural history of its resolution.

There was no suggestion that efficacy was increased by this approach despite animal models suggesting otherwise [6]. Supporting this conclusion, an in vivo study based on hetero-transplanted testicular cancer cell lines found no significant difference in anti-tumour activity or toxicity on histological examnination between continuous or bolus application of bleomycin where the same cumulative doses were compared [11].

Pulmonary toxicity from bleomycin may be related to peak levels and one weakness of this study was failure to measure these – it is possible that the infusion produced higher levels than anticipated and that a more prolonged infusion might have reduced toxicity.

This was a pragmatic study – high resolution CT scanning was not used to assess pulmonary toxicity on the basis that we were not looking for a test to be more sensitive but wanted to assess clinically more relevant changes. It could be argued that the varying scan protocols and acquisition parameters could have obscured significant differences, but the within-institution randomisation ensured that such bias was minimised. Similarly, subtle changes attributable to bleomycin could have been obscured by normal hypostatic changes, since prone scans were not routinely acquired, but this would be expected to affect subjects in both arms equally and the fact that serial scans were obtained in each patient minimised the likelihood of changes being missed or misinterpreted. Whilst intra-observer variability was controlled for by – re-reporting of blinded scans - a weakness of having only one radiologist reporting all the scans was that the potential role of inter-observational error could not be assessed.

The finding of changes, progressing until the end of treatment and then regressing, offers an opportunity for using early changes as a warning for more severe damage if bleomycin is continued. A recent study confirmed a similar pattern of change in lung damage as seen in TE3 with most of the changes in lung function reversing within 1 year of treatment[13]. They however used changes in diffusion capacity to reduce or omit bleomycin which they felt did not reduce survival. Their study differed in that it included poor and intermediate prognosis patients who would have received 4 cycles of bleomycin. This may be important as many of the factors thought to be associated with subsequent pulmonary toxicity were not borne out in our study. Neither baseline pulmonary, nor smoking history, nor renal function predicted toxicity, however In the case of renal function, most (92%) had an estimated glomerular filtration rate of > 80ml/ min, so although no association was noted it might simply suggest that only significantly impaired renal function increased bleomycin toxicity.

Bleomycin lung toxicity remains unpredictable and can be fatal which can lead to dropping bleomycin to avoid risk. For 3 cycles of cisplatin and etoposide the absence of bleomycin was associated with a poorer survival [14]. It is unclear whether dropping bleomycin can be compensated for by the addition of a 4^{th} cycle of cisplatin and etoposide. One study – underpowered to show a survival difference showed a 5% higher event rate in patients randomized to 4 cycles of cisplatin and etoposide [15].

Pulmonary function testing was not useful to identify patients at risk of developing lung toxicity. It was stipulated in the study that no reductions in bleomycin dosage for asymptomatic changes

in pulmonary function testing should be made. This is not the first time that the value of pulmonary function testing has been questioned [16]. This argues for the abandonment of routine pulmonary function testing, which may avoid patients having their bleomycin omitted.

In our study, early CT scanning after 1 cycle of treatment, rather than pulmonary function testing or smoking history, was best able to identify patients at risk of subsequent lung toxicity.

The symptom assessment questionnaire showed that cough rather than shortness of breath was the most important symptom to assess before administration of bleomycin and if this were noted in the absence of another cause, an early CT of the chest might be performed prior to further administration of bleomycin to establish if pulmonary toxicity had occurred.

The number of treatment failures in each arm (6%) was less than seen in previous randomised studies in this population [1, 2] despite the fact that the median age group was higher (32 years) than in comparable studies. The low level of treatment delays and drug omissions may have been responsible for this. It is important to point out that the overall prevalence of bleomycin induced lung damage was relatively low due to the fact that the study only included patients with good prognosis disease. In patients with more pulmonary disease where the total doses of bleomycin would be greater, risks would likely be higher. In a review by Sullivan et al [4] of patients treated, age, dose (> 300, 000 units) and renal dysfunction were associated with increased risk of damage.

Conclusions:

Bleomycin induced lung damage in patients with good prognosis germ cell tumours occurs independently of the method of delivery. The study supports the abandoning of routine pulmonary function testing both to identify patients at risk or during treatment as a means of detecting deterioration in pulmonary function. Instead, symptoms, especially cough, leading to the early use of CT is preferred. A history of smoking may not be a reason to withhold bleomycin. Whether these findings extend to patients with more advanced disease remains undetermined.

Acknowledgements

We thank the following investigators: Dr J le Vay (Ipswich), Dr M Ostrowski (Norwich), Dr S Nicholson (Southend), and Dr A Champion (Glan Clwyd). We also thank all participating patients and the CRUK experimental cancer medicine centre for support. Funding for trial infrastructure was provided by CRUK and the Orchid charity.

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Appendix:

Figures and Tables

Table 1. Baseline characteristics of study patients

Baseline characteristics	Infusional arm (*N*= 105)		Conventional (Bolus) arm (*N*= 107)	
	n	%	*n*	%
Baseline toxicity (mean (SD))*	0.89 (4.5)		0.78 (2.5)	
Age (years)				
<=30	49	46.7	51	47.7
>30	56	53.3	56	52.3
Age (years) (median (IQR))	31.5 (26.5, 36.0)		31.5 (24.8, 39.1)	
Follow-up (years) (median (IQR))	2.3 (1.9, 3.7)		2.3 (2.1, 3.5)	
Smoking status				
Non-smoker	67	63.8	71	66.4
Smoker	38	36.2	36	33.6
Creatinine clearance				
<=80 ml/min	7	6.7	4	3.7
>80 ml/min	98	93.3	103	96.3

* % of grade ≥1 toxicity at baseline (i.e. changes present prior to treatment)

Table 2. Percentage of patients with various level of CT assessed lung toxicity

	Baseline		*P*	Day 21		*P*	End of treatment		*P*	1-year		*p*	2-year		*P*
	IA[1]	CA[2]		IA	CA		IA	CA		IA	CA		IA	CA	
Any grade	9.5	15.0	0.34	31.5	27.3	0.71	79.8	62.0	0.01	54.3	50.6	0.65	50.9	45.2	0.58
Grade ≥2	0	0	-	4.0	0	0.25	44.7	25.0	0.01	3.7	4.6	1.00	3.6	1.6	0.60
Grade 3	0	0	-	0	0	-	8.2	2.2	0.09	1.2	0	0.48	1.8	0	0.47

[1]IA: Infusional Arm. [2]CA: Conventional Arm.

Table 3. Repeated measures mixed effects models for levels of CT assessed lung toxicity

	% of Grade ≥1 toxicity		% of Grade ≥2 toxicity		% of Grade 3 toxicity	
	Estimated coefficient (Difference)	95% CI	Estimated coefficient (Difference)	95% CI	Estimated coefficient (Difference)	95% CI
Treatment						
Conventional arm	*ref*		*ref*		*ref*	
Infusional arm	1.4	-0.36, 3.16	0.92	0.22, 1.62	0.05	-0.11, 0.22
Baseline toxicity	0.67	0.40, 0.94	0.16	0.04, 0.28	0.002	-0.03, 0.03
Age (years)						
<=30	*ref*		*ref*		*ref*	
>30	4.81	3.04, 6.58	0.84	0.14, 1.55	0.14	-0.03, 0.30
Smoking status						
Non-smoker	*ref*		*ref*		*ref*	
Smoker	0.49	-1.36, 2.34	0.06	-0.68, 0.79	0.11	-0.06, 0.28
Creatinine clearance						
<=80 ml/min	*ref*		*ref*		*ref*	
>80 ml/min	-0.79	-5.26, 3.68	0.15	-1.58, 1.88	-0.03	-0.44, 0.38
CT assessed toxicity						
Day 21	*ref*		*ref*		*ref*	
End of treatment	7.28	5.50, 9.06	2.25	1.55, 2.96	0.17	-0.002, 0.33
1 year post treatment	2.18	0.38, 3.98	0.08	-0.63, 0.79	-0.01	-0.18, 0.16
2 year post treatment	2.14	0.14, 4.14	-		-	

Table 4. Correlation between lung function and lung toxicity

Lung function test		Grade ≥1 lung toxicity					
		Baseline		End of treatment		One year post treatment	
		r	*P*	*r*	*P*	*r*	*P*
Baseline	fvc	0.03	0.7	-0.03	0.7	-0.02	0.8
	fev1	0.01	0.9	-0.13	0.1	-0.09	0.3
	tlc	0.03	0.8	0.02	0.8	0.02	0.8
	tlco	-0.07	0.5	-0.08	0.3	-0.07	0.4
	kco	-0.07	0.4	-0.08	0.3	-0.05	0.5
End of treatment	fvc	-	-	**-0.32**	**<0.001**	**-0.26**	**0.003**
	fev1			**-0.36**	**<0.001**	**-0.27**	**0.003**
	tlc			-0.19	0.06	**-0.22**	**0.03**
	tlco			**-0.35**	**<0.001**	**-0.26**	**0.004**
	kco			**-0.2**	**0.02**	-0.09	0.34
One year post treatment	fvc	-	-	-	-	-0.17	0.11
	fev1					-0.17	0.11
	tlc					-0.07	0.6
	tlco					**-0.21**	**0.04**
	kco					-0.04	0.7

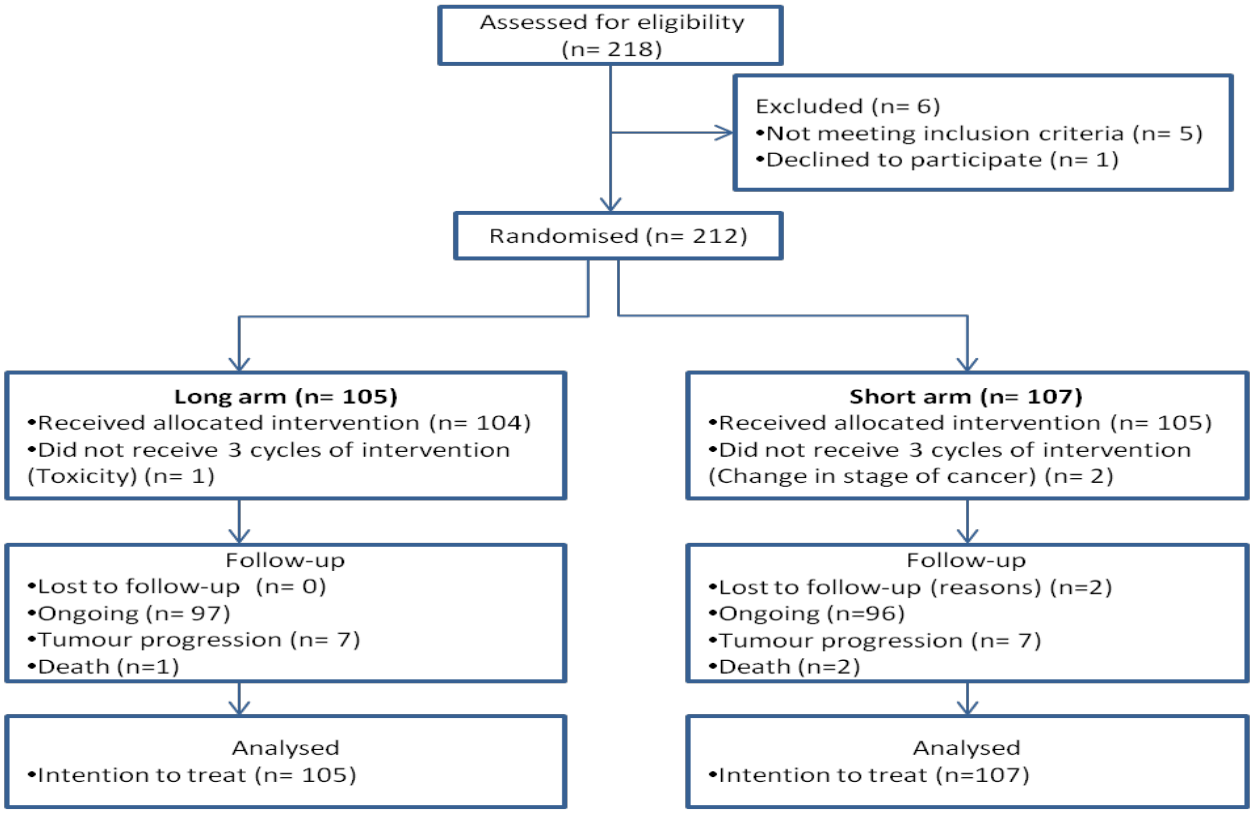
Supplementary Table S1. Simple linear regression analysis results for association between pre-treatment lung function and end of treatment toxicity

	End of treatment toxicity					
	% of Grade ≥1 toxicity		% of Grade ≥2 toxicity		% of Grade 3 toxicity	
Pre-treatment lung function	Regression coefficient	95% CI	Regression coefficient	95% CI	Regression coefficient	95% CI
Baseline fvc	-0.45	-3.08, 2.18	-0.62	-1.84, 0.61	-0.01	-0.16, 0.23
Baseline fev1	-2.58	-5.80, 0.63	-1.1	-2.61, 0.40	0.12	-0.18, 0.41
Baseline tlc	0.28	-2.14, 2.70	-0.17	-1.30, 0.95	-0.05	-0.31, 0.20
Baseline tlco	-0.61	-1.79, 0.58	-0.46	-1.02, 0.09	0.01	-0.10, 0.13
Baseline kco	-3.93	-11.94, 4.07	-1.74	-5.51, 2.03	0.02	-0.74, 0.78

Table 5. Association between symptoms and change of lung toxicity (end of treatment - baseline)

Symptoms	Mean Grade ≥1 % lung toxicity			Mean Grade ≥2 % lung toxicity		
	Better or no change compared to baseline	Worse	*P*	Better or no change	Worse	*P*
Cough	8.3	17.3	**0.001**	1.8	5.9	**0.002**
Cough up mucus	10.4	13.3	0.33	3.0	3.4	0.8
Cough up blood	-	-	-	-	-	-
Tightness in chest	10.7	12.2	0.6	2.6	4.5	0.18
SOB at rest	12.0	7.2	0.16	3.7	0.7	0.09
SOB on walking	11.1	11.4	0.9	3.2	2.9	0.8
SOB on climbing stairs	10.4	12.9	0.36	3.0	3.4	0.8

Supplementary Figure S1: Consort diagram showing study population



Supplementary Figure S2. Trend in toxicity based on lung function tests by arm